DOI: https://doi.org/10.53350/pjmhs22166307

ORIGINAL ARTICLE

Effectiveness of Norethisterone Acetate alone Versus in Combination with Letrozole for treatment of Chronic Pelvic Chronic Pain and Dyspareunia in Patients with Endometriosis

SAIMA ASHRAF[1], AROOJ FATIMAH KHOSA[2], RAHAT FARWA[3]
[1]*Associate Professor of Obstetrics & Gynecology Dept, Nishtar Medical University & Hospital, Multan*
[2]*Senior Registrar of Obstetrics & Gynecology Dept. Ghazi Medical College & Teaching Hospital, Dera Ghazi Khan*
[3]*WMO of Obstetrics & Gynecology Dept, District Head Quarter (DHQ) Hospital, Jhang*
Correspondence to: Dr. Saima Ashraf, Email: saimashahzad35177@gmail.com, Cell # 0311-8443876

ABSTRACT

Aim: To compare mean chronic pelvic pain (CPP) and deep dyspareunia intensity after 6 month treatment of using norethisterone acetate alone and combination with letrozole in patients with endometriosis.
Study design & duration: This randomized controlled trail was conducted from February 1st, 2020 to January 31st, 2021.
Setting: Department of Obs. &Gynecology, Nishtar hospital Multan.
Materials and methods: Seventy two women with age range 18-60 years regardless of parity, having endometriosis with baseline pain > 5 at visual analogue scale were included in study. Pain was measured on VAS at baseline and after 6 months of treatment. All data was entered in a pre-designed proforma.
Results: Mean age of cases was 39.83 ± 12.61 years in group-A and 41.58 ± 12.66 years in group-B. At baseline the mean chronic pelvic pain in group-A was 7.17 ± 1.28 and in group-B was 7.00 ± 1.39. The mean chronic pelvic pain at 6th month was statistically lower in group-A (1.72 ± 0.74) when compared with group-B (4.39 ± 0.64) with a p-value < 0.001. Similarly, deep dyspareunia was markedly reduced follow-up in both group A and group B at 6 months.
Conclusion: CPP and deep dyspareunia are significantly reduced after 6 month of treatment with combined oral letrozole (2.5 mg/day) and norethisterone acetate (2.5 mg/day).
Keywords: Endometriosis, aromatase inhibitor, letrozole, norethisterone acetate.

INTRODUCTION

Endometriosis is a disease characterized by the ectopic presence of endometrial gland and stroma. This condition is dependent on estrogen and estradiol and causes accelerated growth of ectopic endometrial tissue and inflammation.[1,2] In endometriosis, ectopic endometrial tissue behaves like a normal endometrial tissue. With each menstrual cycle, this ectopic endometrium is broken down and it bleeds but due to abnormal location of the tissue it has no way of exit, so it becomes trapped. When this disease involves the ovaries, it causes cysts formation which are named endometriomas. When this whole process involves adjacent tissues like peritoneum, urothelial mucosa etc., it causes irritation of these structures and finally produces scarring and adhesions. As a result bands of fibrous tissue are formed which lead to sticking of pelvic tissues and organs with each other.

Endometriosis is responsible for infertility in 5%–50% of women and causes chronic pelvic pain in >33% women.[3] Endometriosis typically causes heavy regular cycles, deep dyspareunia, dysmenorrhea, pelvic pain unrelated to menstrual cycle and dysuria. [4] Multiple medical treatment options are in use for treatment of endometriosis including combined oral contraceptive pills, medroxyprogesterone acetate, letrozole, danazol, gestrinone and gonadotropin-releasing hormone agonists (aGnRHs).[4] In addition to this there are numerous studies encouraging role of aromatase inhibitors for decreasing severity of symptoms of pain due to endometriosis. Recently, a novel treatment for endometriosis using oral contraceptive and aromatase inhibitor has been developed, however, the action of the double-drug did not allow to determine which treatment is acting to alleviate pain sensations.[5]

Aromatase inhibitors (AIs) are classified into three generations. Letrozole, a third-generation NS aromatase inhibitor, inhibits aromatase selectively. Letrozole brings a pronounced decrease of total body estrogen and currently it is being very broadly utilized for treatment of estrogen receptor positive breast cancer. [6, 7]

Current study is intended to compare effectiveness of letrozole acetate alone and and in combination with norethisterone for relieving pain caused by endometriosis in our local population. So far there is no data available on compareison of this treatment regime for pain relief of endometriosis in our female population. This study will surely generate baseline data and will help us in future to use the better treatment modality for the pain relief in endometriosis.

MATERIALS AND METHODS

This randomized controlled trail was carried out in department of Obs. & Gynecology, Nishtar hospital Multan, over a period of 1 year (from 1st February, 2020 to 31st January, 2021) after approval from ethical review committee. Non-probability purposive sampling technique was used for sample collection. Women with age range 18-60 years regardless of parity, having endometriosis with baseline pain > 5 at visual analogue scale were included in study. However**,** all women having ovarian endometrioma of >3 cm (on USG), uropathy or endometriotic nodules infiltrating muscular layer of bowel wall, using therapies for endometriosis other than NSAID's in the last 3 months, seizure disorder, osteopenia and pregnancy were excluded from study. Data from all cases was recorded after taking informed consent. Basic demographic information, such as age, parity, contact details, weight, height, and BMI were noted. All cases were divided randomly into 2 group using lottery method. In group-A females were treated with oral letrozole (2.5 mg/day) and norethisterone acetate (2.5 mg/day) combination. In group-B females were treated with oral norethisterone acetate (2.5 mg/day). Treatments commenced on first day of menstruation and lasted for six months. Pain was noted on VAS at baseline, 1st month and at 6 month of treatment. Data was entered in pre-designed proforma and analyzed using SPSS version 24. Mean and SD were used for quantitative variables such as age, baseline pain and pain at 6th months, duration of endometriosis, weight, height and BMI. Qualitative variables like parity, marital status, and obesity were measured in terms of frequency and percentage. Data was stratified for age, parity, baseline pain, duration of disease and obesity. Post stratified independent sample t-test was applied and p-value ≤ 0.05 was taken as significant.

RESULTS

The mean age of cases in group-A was 39.83 ± 12.61 years and in group-B it was 41.58 ± 12.66 years. In group-A, 25(69.44%) females had parity <2 and 11(30.56%) cases had parity > 2 while in group- B 22(61.11%) cases had parity < 2 and 14(38.89%) cases had parity > 2. The mean weight, height and BMI in group-A

was 71.56 ± 13.27 kg, 1.64 ± 0.12 m and 26.78 ± 5.19 and in group-B the mean weight, height and BMI was 70.50 ± 11.39 kg, 1.65 ± 0.10 and 26.14 ± 4.71 respectively. In group-A, 8(22.22%) females were obese and 28(77.78%) females were non-obese while in group-B, 6(16.67%) females were obese and 30(83.33%) females were non-obese. The mean duration of endometriosis in group-A was 6.03 ± 2.96 months and in group-B was 6.89 ± 2.59 months as shown in the table 1.

At baseline the mean pain intensity in group-A was 7.17 ± 1.28 and in group-B was 7.00 ± 1.39 as shown in table 2. At 1 month following therapy, the severity of chronic pelvic discomfort and profound dyspareunia was considerably reduced in both group A (p.05) and group B (p.05) compared to baseline levels. The mean CPP intensity at 6 month was statistically lower in group-A (1.72 ± 0.74) when compared with group-B (4.39 ± 0.64). There was significant improvement in CPP in Group-A i.e. p-value < 0.001. In both groups A and B, the severity of deep dyspareunia was dramatically reduced at 6 months follow-up. When stratification of CPP intensity reduction was done against age, parity status, obesity, duration of endometriosis, it was noticed that for all ages, parity status, BMI levels and durations of endometriosis the improvement in mean pain intensity was statistically more pronounced in group-A as compared to group-B with a p-value < 0.01.

Table-1: Descriptive statistics of weight (kg), Age (years), BMI and duration of endometriosis in both groups

	Study Groups	Mean	S.D	Minimum	Maximum
Weight(Kg)	Group-A	71.56	13.27	47.00	96.00
	Group-B	70.50	11.99	50.00	101.00
Age(Years)	Group-A	39.83	12.61	18.00	60.00
	Group-B	41.58	12.66	18.00	60.00
BMI(Kg/m^2)	Group-A	26.78	5.19	19.44	37.78
	Group-B	26.14	4.71	18.52	35.16
Duration of endometriosis (months)	Group-A	6.03	2.96	2.00	10.00
	Group-B	6.89	2.59	2.00	10.00

Table-2: Intensity of CPP and deep dyspareunia at baseline and 6 months of treatment

Symptom	Duration of treatment	Group A	Group B	P-value
Chronic pelvic pain	Baseline	7.19 ± 1.28	7.00 ± 1.39	0.001
	1 month	3.61 ± 1.43	4.96 ± 2.03	
	6 month	1.72 ± 0.74	4.39 ± 0.64	
Deep dyspareunia	Baseline	6.0 ± 1.9	6.4 ± 2.0	0.001
	1 month	2.9 ± 0.8	3.9 ± 1.5	
	6 month	1.6 ± 1.3	2.7 ± 1.7	

Table-3: Stratification of Mean pelvic pain with Age, Parity, BMI and Duration of endometriosis in both groups

			AGE GROUP YEARS		PARITY		BMI		DURATION OF ENDOMETRIOSIS	
			18-39	*40-60*	0-2	>2	Obese	Non Obese	*< 4 weeks*	*≥4 weeks*
PAIN IN 6 MONTHS	Mean	Group A	1.67	1.76	1.72	1.73	1.75	1.71	1.91	1.64
		Group B	4.53	0.70	4.36	4.43	4.00	4.47	4.67	4.33
	S.D	Group A	0.82		0.72	0.79	0.89	0.71	0.83	0.70
		Group B	0.51		0.66	0.65	0.00	0.68	0.52	0.66
	t-test		-12.016	-11.030	-12.896	-9.436	-6.154	-15.035	-7.330	-14.650
	p-value		<0.001**	<0.001**	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

DISCUSSION

Endometriosis is a condition in which the endometrial gland and stroma grow outside of the uterus. This condition is dependent on estrogen and estradiol causes accelerated growth of ectopic endometrial tissue and inflammation.[1,2] In endometriosis, ectopic endometrial tissue behaves like a normal endometrial tissue. With each menstrual cycle, this ectopic endometrium is broken down and it bleeds but due to abnormal location of the tissue it has no way of exit, so it becomes trapped. When this disease involves the ovaries, it causes cysts formation which are named endometriomas. When this whole process involves adjacent tissues like peritoneum, urothelial mucosa etc., it causes irritation of these structures and finally produces scarring and adhesions. As a result bands of fibrous tissue are formed which lead to sticking of pelvic tissues and organs with each other.

Although current medical treatments do not completely eliminate endometriotic lesions, they show effective and safe reduction in sensation of pain. Existing hormonal treatments or conservative surgeries cause pain relief in only 50% of patients with endometriosis [9]. Pathogenesis of endometriosis has widely been studied at molecular and cellular level over last 20 years. Based on these researches, new medical treatment options have been considered for endometriosis.[5] AIs inhibit the production of oestrogen in the ovaries and other organs. When these medications are given to premenopausal women as monotherapy, gonadotrophin secretion increases while oestrogen production decreases, resulting in less oestrogen negative feedback to the brain and pituitary. The stimulation of ovarian activity is caused by gonadotrophins [10].

Studies in which combination of ovarian suppressive agents and aromatase inhibitors have been used for endometriosis treatment are conducted worldwide[10]. Zhao Y et al.[11] noticed that CPP and deep dyspareunia intensity to be significantly decreased after 6th month treatment both in Letrozole and Desogestrel group ($p < .05$) and in Desogestrel group ($p < .05$) however CPP intensity was significantly lower at 6-month in Letrozole and Desogestrel group as compared to Desogestrel. These results are very much similar to our results.

According to a RCT, after conservative surgery for endometriosis, the combination of GnRH analogue and aromatase inhibitor for 6 months is more effective than GnRH analogue monotherapy in improving the pain-free interval and lowering pain recurrence rates.[12] In this study, GnRH analogue is used as ovarian suppressive agent while we used norethisterone as ovarian suppressive agent. However, the results are almost alike. Ferrero s et al have also produced similar results[5]. Other research suggests that AIs not only alleviate pain sensations but even eliminate the illness as an alternative to surgery or as a post-operative recurrence prevention[13]. Remorgida V et al. identified that desogestrel and letrozole combination induces relief of pain symptoms in patients with endometriosis refractory to all other treatment modalities[14]. Aliwadi RK et al. proved that in patients with laparoscopically visible and histologically confirmed endometriosis letrozole and norethindrone acetate combination resulted in significant reduction of pain symptom.[15]. A prospective study conducted on 82 women with pain associated with rectovaginal endometriosis has proven that NETA (norethisterone) combined with Letrozole has been more effective than NETA alone to reduce dyspareunia and pain but with this combined regime higher incidence of side effects without patient satisfaction has been noticed.[16] In one study, where letrozole was used along with progestogen endometrioma volume was reduced to almost 75%and there was marked improvement in pain symptom after 3 months of treatment.[17]

In another study, letrozole alone produced marked reduction in endometrioma volume but the effect was more pronounced when letrozole was combined with NETA.[17] Abushahin F et al.[18] in a multicenter US based study have proven Letrozole to be useful

in treatment refractory endometriosis, however they also noticed that disease recurs after treatment is discontinued. All these studies are in coherence with our findings. The effect of Letrozole is comparable to oral contraceptive pills in management of pelvic pain associated with endometriosis[19]. Rozati R et al.[20] also found that the role of aromatase inhibitors to be equivalent to other hormonal treatments. The most of the studies conducted to date have used aromatase inhibitor for 6 months, we also recommend 6 months periods as initial duration of therapy. For those patients who respond well and have good compliance to medication, a longer treatment duration should be considered. However more studies need to be conducted to find out minimum effective dosage, optimum treatment duration, long-term maintenance therapy need and the role of combination therapy using either oral contraceptives or GnRH analogues. At the same time a placebo effect cannot be overlooked in our study or in previously published studies.

CONCLUSION

It was concluded from our study results that mean pain after 6 months of treatment was significantly lower in the group in which combination of letrozole and norethisterone was used.

REFERENCES

1. Pavone ME, Bulun SE. Aromatase inhibitors for the treatment of endometriosis: a review. Fertil Steril. 2012;98(6):1370–1379.
2. Verma A, Konje JC. Successful treatment of refractory endometriosisrelated chronic pelvic pain with aromatase inhibitors in premenopausal patients. Eur J Obstet Gynecol Reprod Biol. 2009;143(2): 0–115.
3. Abu Hashim H. Potential role of aromatase inhibitors in the treatment of endometriosis. Int J Womens Health. 2014;6:671-80.
4. Zito G, Luppi S, Giolo E, Martinelli M, Venturin I, Di Lorenzo G, et al. Medical treatments for endometriosis-associated pelvic pain. Biomed Res Int. 2014;2014.
5. Ferrero S, Venturini PL, Ragni N, Camerini G, Remorgida V: Pharmacological treatment of endometriosis: experience with aromatase inhibitors. Drugs 2009, 69:943-952.
6. Bourdel N, Alves J, Pickering G, Ramilo I, Roman H, Canis M. Systematic review of endometriosis pain assessment: how to choose a scale? Human Reproduct Update. 2014;21(1):136-52.
7. Madny EH. Efficacy of letrozole in treatment of endometriosis-related pain. Midd East Fertil Soc J. 2014;19(1):64-8.
8. de Ziegler D, Mattenberger C, Luyet C, Romoscanu I, Irion NF, Bianchi-Demicheli F. Clinical use of aromatase inhibitors (AI) in premenopausal women. J Steroid Biochem Mol Biol. 2005;95(1-5):121-7.
9. Vercellini P, Cortesi I, Crosignani P. Progestins for symptomatic endometriosis: a critical analysis of the evidence. Fertil Steril. 1997; 68:393–401
10. Amsterdam LL, Gentry W, Jobanputra S, Wolf M, Rubin SD, Bulun SE. Anastrazole and oral contraceptives: a novel treatment for endometriosis. Fertil Steril. 2005;84(2):300-4.
11. Zhao Y, Luan X, Wang Y. Letrozole combined with oral contraceptives versus oral contraceptives alone in the treatment of endometriosis-related pain symptoms: a pilot study. Gynecological Endocrinology. 2020; 37(1):51-55.
12. Soysal S, Soysal ME, Ozer S, et al. The effects of post-surgical administration of goserelin plus anastrozole compared to goserelin alone in patients with severe endometriosis: a prospective randomized trial. Hum Reprod. 2004 Jan;19(1):160–167.
13. Shippen ER, West Jr WJ. Successful treatment of severe endometriosis in two premenopausal women with an aromatase inhibitor. Fertil Steril. 2004;81(5):1395-8.
14. Remorgida V, Abbamonte HL, Ragni N, Fulcheri E, Ferrero S. Letrozole and norethisterone acetate in rectovaginal endometriosis. Fertil Steril. 2007;88(3):724-6.
15. Ailawadi RK, Jobanputra S, Kataria M, Gurates B, Bulun SE. Treatment of endometriosis and chronic pelvic pain with letrozole and norethindrone acetate: a pilot study. Fertil Steril. 2004;81(2):290-6.
16. Ferrero S, Venturini PL, Gillott DJ, Remorgida V. Letrozole and norethisterone acetate versus letrozole and triptorelin in the treatment of endometriosis related pain symptoms: a randomized controlled trial. Reproductive Biology and Endocrinology, 2011; 9(1): 1-7.
17. Agarwal SK, Foster WG. Reduction in endometrioma size with three months of aromatase inhibition and progestin add-back. BioMed Research International, 2015; 1: 2015.
18. Abushahin F, Goldman KN, Barbieri E, Milad M, Rademaker A, Bulun SE. Aromatase inhibition for refractory endometriosis-related chronic pelvic pain. Fertility and sterility. 2011 Oct 1;96(4):939-42.
19. Bedaiwy MA, Alfaraj S, Yong P, Casper R. New developments in the medical treatment of endometriosis. Fertility and sterility, 2017; 1, 107(3): 555-65.
20. Rozati R, Minhaj H, Nidadavolu N, Balaji AB, Gautam AM. MANAGEMENT OF ENDOMETRIOSIS: AN ENIGMATIC DISEASE. World Journal of Pharmaceutical Research.2020; 15(9): 267-89..